

In the specification, in relation to the paragraph numbers of the published application, US 2005/0287168 A1:

[0002] This invention relates to the germination of spores and in particular, ~~but not exclusively~~, to spores of *Bacillus* species of bacteria and uses thereof.

[0010] It is an aim of the present invention to provide a spore in which said spore may be genetically modified to produce a medicament-therapeutically active protein upon germination into a vegetative cell.

[0011] Accordingly, the present invention, provides *Bacillus* spores which comprise a promoter and at least one genetic construct that is under the control of the promoter and that encodes a therapeutically active compound and: a signal sequence or for said protein; a vegetative cell protein of said *Bacillus*; or the rRNA of the *rrnO* gene, wherein the spore is suitable for use in oral administration for therapeutic treatment. ~~and at least one genetic construct encoding a therapeutically active compound and a sequence or a vegetative cell protein.~~

[0013] It is a further advantage of the invention that the spores elicit an immune response at the mucosal membranes. This makes the vaccination more effective against mucosal pathogens e.g. *S. typhi*, *V. cholera* and *M. tuberculosis*. Thus, the antigen may be derived from a mucosal pathogen.

[0015] It is a further advantage of the present invention in that when said spore is administered to an animal, said spore germinates into a vegetative cell, said vegetative cell expresses said chimeric gene, wherein said chimeric gene ~~comprises said medicament and said protein~~ encodes an antigen in order to elicit an immune response against said antigen.

[0017] Preferably the therapeutically active ~~compound-protein~~ is an antigen or a medicament or a precursor to an antigen or a medicament. Preferably the gene construct is a chimeric gene. Preferably the The spore is of *Bacillus*. ~~or Clostridia.~~

[0019] The gene construct may be under the control of one or more of, each or independently, an inducible promoter, a promoter or a strong promoter or modified promoter. The gene construct may have one or more enhancer elements or upstream activator sequences and the like associated with it.

Between [0028] and [0029], insert the following new paragraph:

--The antigen may be tetanus toxin fragment C or labile toxin B sub unit.--

[0029] The protein used may be any that are expressed only in the vegetative state. The protein may be expressed in the cell barrier or is a soluble cytoplasmic vegetative cell protein. The protein may be a protein that is expressed in the cell barrier.

[0032] The antigen may be a chimera with different vegetative cell proteins. By having the genetic construct encoding the antigen with a genetic construct encoding one or more different vegetative cell proteins it may be possible to provide a temporal expression of the antigen. For example, the medicament-therapeutically active protein may be expressed as a chimera with a vegetative cell protein that is expressed all the time, e.g. OppA or, alternatively the rRNA of rrnO, therefore providing a constant "dose" of antigen.

[0033] Alternatively, the genetic construct encoding the antigen may be with a genetic construct encoding a vegetative cell protein that is expressed intermittently and therefore upon expression of the chimera said chimera is capable of administering the medicament therapeutically active protein in a time-controlled manner. The genetic construct encoding the medicament-therapeutically active protein may also be with a genetic construct of a vegetative cell protein that is expressed initially at a high concentration but which then decreases over time, thus upon expression, the chimera is capable of administering an initial high dose of the antigen.

Between [0033] and [0034], insert the following new paragraph:

--The vegetative cell protein may be one which is expressed all the time or intermittently in the vegetative cell.--

[0035] Alternatively, the genetic construct encoding the antigen may be with a genetic construct encoding a soluble cytoplasmic vegetative cell protein, e.g. or the rRNA from rrnO.

[0038] According to a second aspect, the present invention provides a spore which is genetically modified with genetic code comprising a genetic construct encoding an antigen and a signal sequence, wherein said The invention may employ a signal sequence which directs the therapeutically active protein for secretion or for post-translational processing by vegetative cells of the Bacillus. The signal sequence is may be adapted to target said antigen to a specific part of the vegetative cell. For example, the signal sequence may direct the medicament for secretion, for example active secretion (Type I, Type II or Type III secretion), or for post-translational processing by the vegetative cell, e.g. glycosylation.

[0044] According to a further aspect, the present invention provides spores according to the invention in which said spore is genetically modified with genetic code comprising comprises at least one genetic construct that is under the control of a promoter and that encoding encodes a medicament-therapeutically active protein and a vegetative cell protein, as a chimeric gene.

[0045] The medicament-therapeutically active protein may be one or more of:

[0052] According to a third aspect, the present invention provides a pharmaceutical composition for oral administration comprising Bacillus spores of the invention in association with a pharmaceutically acceptable excipient or carrier, comprising a spore according to the invention in association with a pharmaceutically acceptable excipient or carrier.

[0054] According to a further aspect, the present invention provides a composition according to the invention for use in a method of medical treatment. Bacillus spores of the invention for use in the treatment of the human or animal body by therapy.

[0055] The invention also provides use of the composition according to the invention in the manufacture of the medicament for use in the treatment of a medical condition. Bacillus spores of the invention in the manufacture of a medicament for the treatment of cholera, typhoid, tuberculosis, tetanus or E. Coli infection.

[0056] A method of medical treatment would comprise treating a medical condition e.g. a disease or administering Medicaments may be administered as a vaccine. Medical conditions for treatment by the invention include, for example, inflammation, pain, hormonal imbalances and/or intestinal disorders.

[0057] According to a further aspect, the present invention provides a method of medical treatment, which method comprises the steps of Administration of medicaments of the invention may involve:

[0058] a) Orally administering a spore according to the invention Oral administration to a person or animal in need of medical treatment;

[0059] b) Said spore The spores germinating into a vegetative cell in the intestinal tract;